REMARKS

Reconsideration of the application and allowance of all pending claims are respectfully requested in light of the remarks provided below. Claim 1-29 are currently pending with claims 6-19 being withdrawn from consideration because of a restriction requirement.

In accordance with 37 C.F.R. 1.121(c)(1)(ii), a marked-up version of the amended claims is provided on one or more pages separate from the amendment. These pages are appended at the end of the Response.

I. Request for Additional Prior Art

In the Office action, the Examiner requests an exact publication date for each of the 1996 articles (Advanstar and the Drug Manufacturing Technology Series, Vd.2) to ascertain their prior art status as to this application. Applicants respectfully submit that both of these 1996 articles are prior art. In fact, the Advanstar publication includes a footnote on the first page of the article stating that the article was previously published at a convention in February 1992.

The Examiner also asserts that Applicants have not fully disclosed the prior art. Specifically, the Examiner requests further disclosure of the prior art discussed in the "Description of Prior Art" section in the specification of the above-identified application. In response to an Office action issued in SN 08/895,936, Applicants submitted the Second Declaration of Richard Wisniewski in response to this same inquiry. A copy of this declaration is submitted herewith.

Applicants respectfully submit that the first two paragraphs in the "Description of Prior Art" section in the specification on page 2 of the present invention refer to the 1992 Genentech device disclosed in the 1992 Wisniewski and Wu publication. See Second Declaration of

Richard Wisniewski, ¶8, submitted herewith. Applicants also submit that the prior art described in the third paragraph of this section refers to a device having ribs welded to both the core and the interior wall of the vessel. See Second Declaration of Richard Wisniewski, ¶9, submitted herewith. Since the ribs were connected to both the internal core and the interior wall of the vessel, heat transfer occurs only through the external wall of the vessel. Such vessels can be used in heat storage devices for, e.g., paraffin. Id. Although not relevant to the particular freezing of biopharmaceutical materials, an example of such vessels in which the ribs are connected to the core and the interior wall is found in U.S. Patent Nos. 2,441,376 to Stiening and 2,129,572 to Finnegan.

The Examiner also requests Applicants disclose how close the heat transfer fins extend to the wall of the container, the dimensions of those fins, the diameter of the container and the volume of the container of the 1992 Genentech device. However, contrary to the Examiner's indication in the Office action, Applicants are not in possession of the 1992 Genentech container or additional material information relating to the container (e.g. diameter, volume of container, dimension of the fins, how close to the wall of the container the heat transfer fins extended) not already disclosed in the 1992 Wisniewski and Wu article. Applicants do not work for Genentech, which, presumably, has exclusive control of the containers and information related to the containers, if such container or information still exists. Therefore, Applicants have no way to obtain actual measured results or computer generated results of the 1992 Genentech container.

Although he does not remember the exact distance between the fin tip and the interior wall of the 1992 Genentech device, Mr. Wisniewski does state in his second declaration, submitted herewith, that there was a large gap between the fin tips and the interior wall of the

1992 Genentech vessel (e.g. greater than 4 inches). Applicants respectfully submit and reiterate that all information in their possession and knowledge concerning the 1992 Genentech container disclosed in the 1992 Wisniewski and Wu article has been disclosed to the U.S. Patent Office. Moreover, this information, especially the proximity of the fins to the interior wall of the container, is not recited in the claims of the instant application.

Instead, the present application, in one aspect, is directed to a method for preserving a biopharmaceutical product. The method comprises placing a medium comprising a biopharmaceutical product within a vessel having an interior cavity defined by an interior wall of the vessel. The method also comprises flowing a cooling fluid through a removably mounted heat exchange structure comprising an elongated pipe having a central axis. At least a portion of the central axis of the elongated pipe is positioned coaxially with the central axis of the vessel within the cavity. The structure has one or more heat transfer members thermally coupled to the structure. The method also comprises actively cooling the interior wall using a fluid.

II. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-5 and 20-29 stand rejected under 35 U.S.C. §112, second paragraph. Specifically, the Examiner considers the term "biopharmaceutical product" to be ambiguous. Applicants respectfully traverse this rejection.

First, Applicants did not provide a definition in the specification for the term "biopharmaceutical product." Instead, Applicants provided a number of examples of the type of biopharmaceutical products that may be processed by the present invention. The term "biopharmaceutical product" as set forth in the Specification on page 20 includes, but is not limited to, proteins, cells, antibodies, medicines, plasma, blood, buffer solutions, viruses, serum,

cell fragments, cellular components, and any other biopharmaceutical product.

Applicants also provided a definition of a "biopharmaceutical product" in a previous Amendment dated April 13, 2000 submitted in Application Serial No. 08/895,936 as "a product derived from biological sources that has an intended therapeutic application and whose manufacturing is or will be regulated by pharmaceutical or veterinary regulatory agencies." This definition is supported by the Declarations of Chris J. Burman, V. Bryan Lawlis, Jr., and David A. Vetterlein ("the Declarants"), who are considered by Applicants as persons of ordinary skill in the art.

Despite support of the aforementioned understanding of the term of "biopharmaceutical products" from three persons of ordinary skill in the art having over 72 years of experience in the biotechnology and biopharmaceutical industry, the Official Action, as read, erroneously complicated the well recognized understanding of this term. For example, the Office Action sets forth an opinion in concluding that orange juice and milk are biopharmaceutical products. In particular, the Examiner makes an unsupported statement in the Office Action on page 7 that "[b]lood *would probably* freeze more in the manner of orange juice or milk given its nearly macroscopic cellular nature whereas viris in a suitable buffer solution or water would freeze in the manner of pure or salty water." (emphasis added). Based on such reasoning and unsupported statements, the Official Action indicates that the definition offered by the Declarants appears to be unworkable. (See page 7 of the Office Action). However, when not defined by an applicant in the specification, the words of a claim must be read as they would be interpreted by those of ordinary skill in the art, MPEP 2111.01, not by the Examiner himself.

In the Office action, the Examiner suggests that nothing in the declarations address why

one designing freezing equipment for biopharmaceutical products disclosed in the specification would not look to the art of freezing water, orange juice or solids suspended in liquids. To the contrary, this issue has been addressed numerous times in previous responses in co-pending application and in the specification. As provided in the Specification, Applicants recognized, among other things, that the apparatus and method according to the aspects of the present invention are suited for use in processing biopharmaceutical products, as that term is understood by those of ordinary skill in the art. For example, the recited apparatus and method promotes uniform freezing at a rapid pace which allows the biopharmaceutical product in the container to be frozen in as close to its native state as possible. (Specification, page 7, lines 17-19). Additionally, the present invention allows the freezing process to be done in a repeatable fashion so that a user can be assured that the freezing process is not causing batch to batch variations in the product. (Specification, page 7, lines 19-21).

Applicants respectfully submit that improper processing of biopharmaceutical product by, such as, for example, freezing and thawing, destroys biopharmaceutical products. In contrast, other products, such as, for example, orange juice, milk, water, particulate materials, and comestibles do not have the same processing concerns as biopharmaceutical products. Therefore, such products as orange juice, milk, water, particulate materials and comestibles, which do not require uniform freezing at a rapid pace which allow them to be frozen in as close to its native state as possible in order to prevent damage, are not included in the definition of biopharmaceutical products. In particular, the method or apparatus used to process (e.g. freeze or thaw) these other products is not critical and will not destroy these other products.

Applicants, however, recognize that, for example, a "buffer solution" can indeed be a

biopharmaceutical product depending upon the contents of such a solution. In lab chemistry, buffers are associated with the maintaining of certain pH levels, while biopharma vocabulary (which is relevant to this application) uses the term buffers very broadly, including buffers with proteins (like Human Serum Albumin) or amino acids (multiple amino acids are used, for example, lysine or arginine) clearly having biomolecules which can be damaged by improper freezing. It is readily apparent that buffer solutions which are biologically based may indeed be regulated and be a biopharmaceutical product. Applicants respectfully submit that if, for example, a particular buffer solution is not derived from biological sources nor regulated by FDA, then it would not be considered a biopharmaceutical product under the aforementioned understanding of the term. Once one recognizes that the list of potential biopharmaceutical products provided in the specification sets forth examples of products which may be biopharmaceuticals, it is readily apparent to one of ordinary skill in the art what the term "biopharmaceutical product" means.

Therefore, Applicants respectfully traverse the opinion set forth in the Office Action that orange juice, milk, water, comestibles, particulate materials and any other non-biopharmaceutical products (e.g. orange juice and milk) relied upon by the Office Action are considered a biopharmaceutical product and that vessel that freeze such materials are relevant to the delicate preservation of biopharmaceutical products. To maintain such a rejection, the Office, under M.P.E.P. § 2144.04, must be supported by a reference or affidavit in support of such position and opinion or in contradiction to the above definition and Declarations by three Declarants of ordinary skill in the art. Specifically, the Office must show that products such as orange juice, milk and comestibles require uniform freezing at a rapid pace which allow them to be frozen in

as close to its native state as possible in order to prevent damage. To date, the Examiner has failed to provide such proof.

Moreover, as stated in previous correspondence with the Examiner, any of the exemplary biopharmaceutical products provided in the Specification, or any other biopharmaceutical products, must be a biopharmaceutical product according to the above definition, having the same processing concerns. Applicants respectfully submit that one of ordinary skill in the art is capable of distinguishing and classifying which products are and are not biopharmaceutical products based on the above definition, as evidenced by, for example, the Declarants classification of milk and orange juice as not being pharmaceutical products in their Declarations. For example, one of ordinary skill in the art is capable of determining which proteins, cells, antibodies, medicines, plasma, blood, buffer solutions, viruses, serum, cell fragments, cellular components, and any other biopharmaceutical product are considered a biopharmaceutical product under the above definition.

Finally, Applicants object to the reliance in the Office Action on an interpretation of a "would-be infringer" in rejecting the term "biopharmaceutical products." Under M.P.E.P. § 2173.02, definiteness of claim language must be analyzed in light of the content of the particular application disclosure, the teachings of the prior art and the claim interpretation that would be given *by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.* Applicants respectfully submit that the proper inquire is how "biopharmaceutical product" will be interpreted by a person of ordinary skill in the art, not a would be infringer.

Accordingly, Applicants respectfully submit that the term "biopharmaceutical product" is definite.

III. Rejection Under 35 U.S.C. §103(a)

Claims 1-5 and 20-29 stand rejected under 35 U.S.C. §103(a) as being unpatetneable over the combined teachings of the 1992 Wisniewski and Wu publication and the 1986 Kalhori and Ramadhyani article entitled "Studies on heat transfer from a vertical cylinder with or without fins, embedded in a solid phase change medium" ("the 1986 Kalhori and Ramadhyani article") and U.S. Patent No. 2,114,642 to West ("the '642 West patent").

Applicant notes the Examiner's rejection based the 1992 Wisniewski and Wu research paper disclosing fins in close spaced proximity to the interior surface of the container and the alleged bridge of ice inherently formed between the tip of the heat transfer fins and the interior of the container. However, Applicant respectfully submits that these limitations are not recited in the claims of the instant application. It appears that the Examiner has repeated his rejections from previous applications which are inapplicable to the instant application. Although the Examiner misinterprets the term "thermal transfer bridge" by equating the same to an ice bridge and interpreting the 1992 Wisniewski and Wu article to show fins in close proximity to the interior wall of the vessel, these features are not relevant to the examination and allowance of the claims in the instant application and thus, will not be addressed by this Response.

The claims of the present invention recite a method of preserving or processing a biopharmaceutical product by placing a medium comprising a biopharmaceutical product within a vessel having an interior cavity. The method also recites flowing a cooling fluid through a removably mounted heat exchange structure within the interior cavity of the vessel. This structure includes an elongated pipe having a central axis. At least a portion of the central axis of the elongated pipe is positioned coaxially with the central axis of the vessel. The pipe has one or

more heat transfer members thermally coupled thereto. The method also requires actively cooling the interior wall using a fluid.

The 1992 Wisniewski and Wu article, the 1986 Kalhori and Ramadhyani article and the '642 West patent, alone or in combination fail to disclose or suggest all of the limitations recited in the claims. For example, the 1992 Wisniewski and Wu article and the '642 West patent fail to disclose or suggest an elongated pipe with at least a portion of its central axis of being positioned coaxially with the central axis of the vessel and the 1986 Kalhori and Ramadhyani article fails to disclose the active cooling of the interior wall using a fluid as required by the claims. Moreover, the method of freezing disclosed in these articles freeze products in totally different ways using different freezing principles.

In the 1992 Wisniewski and Wu article, the Genentech device disclosed includes a freeze-thaw vessel for biopharmaceutical products having an internal heat transfer coil pipe with fins welded to the external surface of the coil pipe, not an elongated straight pipe centrally positioned. The figure in the article accurately depicts the heat transfer coil and fin arrangement within the vessel. The fins attached to the coil are very small and thin and were designed only to aid the freezing around the loop pipe in order to increase the relatively small surface area of the loop pipe (e.g. adding more cold surface area).

The 1986 Kalhori and Ramadhyani article involves the investigation of solidification of a heat storage medium around a smooth vertical cylinder and also a vertical cylinder with fins. However, only the cylinder was cooled during this investigation. The external vessel walls were not actively cooled as required by the claims of the present invention. The cylinder discussed in this article cools and solidifies the medium by building up towards the external walls of the

vessel. Therefore, the temperature from the cylinder (or fin attached to cylinder) to the external wall to increases, as opposed to decrease when the interior wall is actively cooled. Moreover, part of the vessel in this article was wrapped with an electrical ban heater to warm the medium from the outside while the cylinder was cooling it. This cooling and heating generates convectional currents in the liquid phase of the medium. Therefore, the process investigated by Kalhori and Ramadhyani in their 1986 article was completely different from the present invention and the Genentech device disclosed in the 1992 Wisniewski and Wu article. Each of these methods involves different freezing principles resulting in different temperature gradient profiles during freezing, and thus completely different methods and technologies to freeze products.

The '642 West patent is directed to the acceleration of the production of frozen articles such as milk, sherbet and similar substances, not to the preservation of biopharmaceutical products. The '642 West patent describes freezing that prevents sugar deposition from the original solution. The object of this patent is not to optimize the preservation of biopharmaceutical products by freezing, but rather to fast freeze to make milk and sherbet look a certain way (e.g. appealing to consumers). In the '642 West patent, liquid refrigerant gets to the header (3) where it boils in cup (15) onto which the container with product (8) is slipped. Since the refrigerant boils inside the cups (15), then there is no control of freezing (e.g. very fast freezing, see page 2, lines 60-66) as in the case of the present invention having a constant freezing front velocity. The '642 West patent does not show any cooling surface extensions such as fins or an elongated pipe.

Therefore, the 1992 Wisniewski and Wu article, the 1986 Kalhori and Ramadhyani

article, and the '642 West patent, either alone or in combination, fail to disclose or suggest the method and arrangement of the vessel recited in the claims of the present invention. In fact, these articles and the '642 West patent freeze products by completely different ways using completely different principles than the present invention. As such, these references teach away from each other. Specifically, the 1986 Kalhori and Ramadyani article teaches heating the medium from the outside of the cylinder while the structure within was cooling it. In sharp contrast, the 1992 Wisniewski and Wu publication teaches cooling the outside of the cylinder. One of ordinary skill in the art would not look towards a device that is heated on the outside to combine with a device that was cooled on the inside because the methods and principles of freezing used in both devices are completely different. There is simply no suggestion or motivation to combine the structure within the 1986 Kalhori and Ramadyani article with the cooled cylinder of the Genentech device. Further, the '642 West patent discloses a method of freezing completely different from the Genentech device and the 1986 Kalhori and Ramadyani article.

Accordingly, Applicants respectfully submit that the claims are patentable over the cited references.

IV. Conclusion

For these reasons, it is believed that all of the claims as presently presented are patentable, and that this application is in allowable condition. Accordingly, allowance of the

claims is respectfully requested.

Respectfully submitted,

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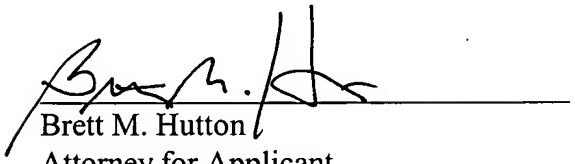

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Version Showing Marked-Up Claims

In the Claims:

Please amend claims 1, 20 and 25 as follows:

1. (Amended) A method of preserving a biopharmaceutical product comprising:

placing a medium comprising a biopharmaceutical product within a vessel having an interior cavity defined by an interior wall of said vessel, said vessel having a central axis;

flowing a cooling fluid through a removably mounted heat exchange structure within said interior cavity of said vessel, said structure comprising an elongated pipe having a central axis, wherein at least a portion of the central axis of said elongated pipe is [being centrally] positioned coaxially with the central axis of the vessel within said cavity, said structure having one or more heat transfer members thermally coupled thereto; and

actively cooling said interior wall using a fluid.

20. (Amended) A method for facilitating the processing of a biopharmaceutical product comprising:

providing a vessel adapted to receive a medium comprising a biopharmaceutical product therein, said vessel having an interior cavity defined by at least an interior wall of said vessel, said vessel having a central axis;

providing a passage for actively cooling said interior wall using a cooling fluid; and

providing a heat exchange structure within said cavity, said heat exchange structure

including an elongated pipe having a central axis, wherein at least a portion of the central axis of said elongated pipe is [being centrally] positioned coaxially with the central axis of the vessel within said cavity, said elongated pipe having one or more heat transfer members thermally coupled thereto, said elongated pipe defining a passage for actively cooling the one or more heat exchange members using a cooling fluid.

25. (Amended) A method of processing a biopharmaceutical product comprising:

providing a vessel adapted to receive a medium comprising a biopharmaceutical product therein, said vessel having an interior cavity defined by an interior wall of said vessel and a heat exchange structure within said cavity, said heat exchange structure having an elongated pipe having a central axis, wherein at least a portion of the central axis of said elongated pipe is [being centrally] positioned coaxially with the central axis of the vessel within said cavity, said elongated pipe having one or more heat transfer members thermally coupled thereto;

placing a medium comprising a biopharmaceutical product within said vessel;

actively cooling said interior wall using a cooling fluid;

actively cooling said heat exchange structure by flowing a fluid through the elongated pipe; and

freezing the medium within said vessel to preserve said biopharmaceutical product.